severe necrotizing pancreatitis and early operative or catheter drainage may result in improved survival rates. The use of prophylactic antibiotics in these patients should be evaluated by a controlled trial.

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Misoprostol Therapy for Patients Taking Nonsteroidal Anti-inflammatory Drugs

GASTROPATHY INDUCED BY the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a major complication of these widely prescribed drugs. Patients at highest risk for gastropathy are those on long-term NSAID therapy, including the elderly, arthritic patients, and those with a history of abdominal pain or gastric intolerance to NSAIDs. The spectrum of gastropathy includes mucosal hemorrhages or erosions, gastric ulcer—present in as many as 15% of the population at risk—and duodenal ulcer, and any of these may present with complications such as gastrointestinal bleeding or perforation. Attempts to prevent NSAID-related gastropathy with H_2-receptor blockers and sucralfate have been unsuccessful, though these agents remain useful for healing established ulcers once NSAID therapy is discontinued.

The mechanism of NSAID-induced mucosal damage is not completely understood. The suppression of mucosal prostaglandin production and a reduction of mucosal blood flow by NSAIDs are contributing factors, and the presence of gastric acid is required. Prostaglandins such as misoprostol, a synthetic prostaglandin E_2 analogue, have been investigated for their role in gastric mucosal protection, particularly against insults such as from taking NSAIDs. In low doses these agents have cytoprotective properties such as enhancing mucosal blood flow and gastric mucous production. In higher doses they can inhibit gastric acid secretion. In healthy subjects misoprostol use has been shown to prevent mucosal lesions induced by NSAIDs and aspirin. Even with doses below antisecretory levels, patients had lowered endoscopic scores of mucosal damage, suggesting cytoprotection by misoprostol. Notably, abdominal pain and other gastrointestinal symptoms were not reduced in these short-term studies.

Two recent trials show the clinical usefulness of misoprostol in arthritic patients on NSAID therapy. One trial enrolled patients with abdominal pain but without gastric ulcers on endoscopy and showed a significantly reduced incidence of gastric ulcer in the group treated with misoprostol. Because the overall incidence of gastric ulcer was high, the study was terminated for ethical reasons before statistically significant data could be collected on the effects on duodenal ulcers. In a second study, misoprostol therapy produced substantial regression of gastropathy in patients with rheumatoid arthritis who continued on aspirin therapy. No exacerbation of arthritic symptoms was noted in patients treated with misoprostol.

Unfortunately, none of these studies have shown any consistent benefit on abdominal symptoms; in fact, some have shown worsened gastrointestinal symptoms in the misoprostol-treated patients. This is due in part to the side effects of the drug, which include diarrhea, dyspepsia, and abdominal pain, and may require reducing the dose from the recommended starting dose of 200 μg four times a day to 100 μg. Misoprostol also has uterotonic effects and may cause cramping, bleeding, or spontaneous abortion, necessitating extreme caution in prescribing to women of childbearing age and contraindicating its use in pregnancy.

Misoprostol therapy should certainly be considered for patients with disabling arthritis who need to continue on NSAID therapy despite a serious complication—such as gastric ulcer or gastrointestinal bleeding—from these agents. It may be indicated in symptomatic patients on NSAID therapy, particularly elderly or chronically ill persons, to prevent the development of gastric complications. Because its efficacy in reducing symptoms has not been shown, assessing any clinical benefit over the short term may be difficult, especially because many of these patients will not be followed up with endoscopy. The role of misoprostol therapy in high-risk asymptomatic patients without documented gastrointestinal complications bears further investigation. Its effects on the prevention and healing of duodenal ulcers need to be assessed. Finally, long-term studies are needed to evaluate the efficacy of misoprostol therapy in preventing more serious complications such as gastrointestinal bleeding and perforation and to identify the patient groups that may benefit from such therapy.

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Rheumatoid Arthritis and Methotrexate—A Renewed Partnership

METHOTREXATE was first used to treat hematologic malignant disorders in the late 1940s. It was later tried in rheumatic diseases with the assumption that the two groups of patients shared a similar pathophysiology. Because of the serious side effects associated with the earlier dosage regimens and the recognition of the dramatic effects of corticosteroids, its use was soon discarded. The modern application of methotrexate began in the 1960s when introduced in the treatment of psoriasis and dermatomyositis.

Since 1980 when an eight-year experience with the use of methotrexate to treat rheumatoid arthritis was described, several authors have published data supporting the relative safety and efficacy of its use in patients with this disorder. In 1988 the American College of Physicians published a "position paper" describing its use, and this year, after 45 years on the market, the Food and Drug Administration approved its use for the treatment of rheumatoid arthritis.

Methotrexate is a folic acid analogue. It inactivates intracellular enzymes, depleting the cell of reduced folates necessary for the formation of purines and pyrimidines and thus DNA. Its mechanism of action in rheumatoid arthritis is un-

known but would appear to include antirheumatic and anti-inflammatory properties. Specific actions described include the suppression of neutrophil chemotaxis and the enhancement of the function of killer cells. Administering leucovorin calcium can reverse clinical improvement, suggesting folate antagonism as a mechanism. No effect on prostaglandins has been reported.

The use of methotrexate should be considered when more traditional methods of treating rheumatoid arthritis, such as gold therapy, have failed. Although the accumulated data suggest that methotrexate as primary therapy may be recommended in the future, long-term follow-up information is not yet available to support the safety of this approach. Moreover, methotrexate has not yet been proved to induce true remissions in these patients. Severe flares of rheumatoid arthritis after discontinuing therapy have been reported.

Because of the potentially severe side effects, candidates for therapy must be selected carefully and monitored continuously. Contraindications include the presence of infection, hepatic disease, alcohol intake, or reduced renal function as estimated by an age-adjusted creatinine clearance. Relative contraindications include either hematologic abnormalities unrelated to rheumatoid arthritis or interstitial lung disease.

The baseline evaluation should include a complete blood count, blood chemistry values, a urinalysis, and a chest roentgenogram in all patients. Regularly scheduled monthly visits with a physician familiar with the drug and a redetermination of blood count and liver function indexes are prudent. The necessity of doing a liver biopsy is controversial, but most reports suggest a biopsy after a cumulative dose of 1,500 mg. Current practice based on accumulated experience is to do a biopsy only if liver enzyme levels remain elevated after stopping the drug. When evaluating a biopsy specimen, the awareness that pretreatment histologic abnormalities have been reported should be kept in mind. Pulmonary function should be assessed if respiratory symptoms develop because methotrexate toxic effects include interstitial pneumonitis. The initial dose is 7.5 mg one day per week with the maximal dose seldom exceeding 15 mg.

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Thrombolytic Therapy for Acute Myocardial Infarction

ADMINISTERING thrombolytic drugs to patients with acute myocardial infarction results in clot lysis and reperfusion of the occluded coronary artery in about 35% to 75% of patients. Successful reperfusion results in enhanced survival and improved left ventricular function, most likely owing to a decrease in infarct size. Furthermore, a reperfused infarct is less likely to undergo remodeling and expansion, resulting in less deterioration of left ventricular function in the days and weeks after infarction. Most trials have shown that initiating thrombolytic therapy early—within three hours after chest pain begins—improves the success of thrombolysis and survival compared with the results of giving thrombolytic therapy relatively late after the onset of chest pain. The Second International Study of Infarct Survival (ISIS-2) trial, however, showed that intravenous streptokinase therapy lengthened survival, even when given 12 to 24 hours after the start of symptoms. This may have been due to the presence of collateral circulation in certain patients, possibly delaying the time after which irreversible myocardial injury occurred. Alternatively, this may indicate that later reperfusion after a completed infarction may be of benefit by preventing infarct expansion. Many of the initial thrombolytic trials emphasized that the major improvement in survival occurred in patients with anterior myocardial infarctions. A trial from New Zealand, however, and the ISIS-2 trial showed that thrombolytic therapy improved survival rates in patients with inferior myocardial infarctions as well.

The possible benefits of coronary reperfusion in patients with acute myocardial infarctions need to be weighed against the side effects of thrombolytic therapy. The most serious side effect of thrombolytic therapy is intracranial bleeding, which occurs in about 0.5% of patients. Other side effects include bleeding from other sites, hypotension, and reperfusion arrhythmias. Streptokinase also has the potential to cause allergic reactions and, rarely, anaphylaxis. Risk factors that would preclude a patient from receiving thrombolytic therapy include the presence of active internal bleeding, a history of a previous cerebrovascular accident, neurosurgical procedure or head trauma, an intracranial neoplasm, an atrioventricular malformation or aneurysm, and a known bleeding disorder. Investigators have excluded patients older than 75 years from receiving thrombolytic therapy because of a perceived increased risk for intracranial bleeding. The ISIS-2 trial, however, showed no increased risk for intracranial bleeding following intravenous streptokinase therapy in patients older than 75 years. Further studies will be necessary to confirm this observation.

Because thrombolytic therapy fails to lyse coronary thrombi in about 25% of patients, coupled with the observed and perceived risks of coronary reocclusion and reinfarction, many investigators have examined the possible role of adjuvant pharmacologic therapy and mechanical reperfusion in patients receiving thrombolytic therapy. The ISIS-2 trial showed that using aspirin reduced mortality by 21% in patients with suspected myocardial infarctions. This reduced mortality was additive to that due to intravenous streptokinase therapy. Aspirin use also decreased the incidence of reinfarction in patients receiving intravenous streptokinase by approximately 50%. The Thrombolysis in Myocardial Infarction (TIMI) phase IIB trial found that the early administration of metoprolol reduced the incidence of recurrent angina compared with late metoprolol administration, starting on day 6 after an infarction. Furthermore, when given within two hours of the beginning of chest pain, metoprolol therapy reduced the combined incidence of nonfatal reinfarction and mortality. In patients with persistent coronary artery stenosis, coronary angioplasty done immediately after thrombolytic therapy results in increased complications and mortality compared with delayed angioplasty—that is, done one to seven days after an infarction. Furthermore, the TIMI phase IIB trial showed that doing angioplasty one to two days postinfarction failed to improve survival or left ventricular function or to reduce the incidence of reinfarction compared